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Naasz, R.; Arnold, L.A.; Minnaard, A.J.; Feringa, B.L.

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Highly Enantioselective Copper-Phosphoramidite Catalyzed Kinetic Resolution of Chiral 2- Cyclohexenones

Robert Naasz, Leggy A. Arnold, Adriaan J. Minnaard, Ben
L. Feringa*

General procedure for the kinetic resolution of **1a**, **1b**,
1d and **3** on an analytical scale:

All resolution were performed on a 1 mmol scale with 1
mol% Cu(OTf)₂ and 2 mol% of the phosphoramidite ligand
with *n*-dodecane as internal standard according to the
general procedure (vide infra).

Typical experimental procedure for the resolution of
racemic **1a** on an analytical scale; In flame dried
glassware under an argon atmosphere 3.6 mg (0.01 mmol)
Cu(OTf)₂ and 10.8 mg (0.02 mmol) (*S,R,R*)-**L1** were dissolved
in 10 ml of dry toluene. After stirring at RT for 1 h the
colorless solution was cooled to -40°C and 110 mg (1.0
mmol) racemic **1a** and 40 μ L *n*-dodecane (internal standard)
were added. After stirring for 10 min 0.73 mL Et₂Zn (1.1 M

in toluene, 0.8 mmol) was added. Samples of 0.2 mL were taken after 2, 5, 10, 15, 20, 25, 30, 45 and 60 min. The samples were quenched in 1 mL Et₂O saturated with water and filtered over a small plug of silica. The silica plugs were thoroughly rinsed with the "wet" Et₂O. Both conversion and ee were determined by chiral GC. Chiraldex G-TA, 50 m × 0.25 mm, He-flow: 1.0 mL/min, 100°C isotherm. T_{ret} 13.4 min (*n*-dodecane), T_{ret} 21.6 min ((*S*)-**1a**), T_{ret} 22.7 min ((*R*)-**1a**).

Determination of conversion and ee for **1a**.

In all cases ee and conversion were determined by GC on a Chiraldex G-TA column (vide supra) except for the resolution performed with Me₂Zn because in this case the peaks of (*S*)-**1a** and addition product showed overlap. *Ee* and conversion were therefore measured on a Chiraldex A-TA column.

Determination of conversion and ee for **1b**.

Ee and conversion were determined by GC on a Hydrodex-B-3P column, 25 m × 0.25 mm, He-flow: 0.9 mL/min. Initial temp: 90°C, initial time: 10 min, rate: 5°C/min, final temp: 150°C. T_{ret} 17.5 min (*n*-dodecane), T_{ret} 21.9 min ((*S*)-**1b**), T_{ret} 22.1 min ((*R*)-**1b**).

Determination of conversion and ee for **1d**.

Ee and conversion were determined by GC on a CP-Chirasil-Dex CB column, 25 m \times 0.25 mm, He-flow: 1.0 mL/min. Initial temp: 125°C, initial time: 20 min, rate: 10°C/min, final temp: 175°C. T_{ret} 6.0 min (*n*-dodecane), T_{ret} 10.9 min ((*S*)-**1d**), T_{ret} 11.4 min ((*R*)-**1d**).

Determination of conversion and ee for **3**.

Ee and conversion were determined by GC on a ChiralDEX G-TA column, 50 m \times 0.25 mm, He-flow: 1.0 mL/min, 100°C isothermic. T_{ret} 13.4 min (*n*-dodecane), T_{ret} 20.1 min ((*R*)-**3**), T_{ret} 20.8 min ((*S*)-**3**).

Procedure for the kinetic resolution of **1c**.

In flame dried glassware under an argon atmosphere 10.5 mg (0.03 mmol) Cu(OTf)₂ and 31.3 mg (0.06 mmol) (*S,R,R*)-**L1** were dissolved in 20 ml of dry toluene. After stirring at RT for 1 h the colorless solution was cooled to -35°C and 1.0 g (5.8 mmol) racemic **1c** and 0.40 mL *n*-hexadecane (internal standard) were added. After stirring for 10 min 2.85 mL Et₂Zn (1.1 M in toluene, 3.1 mmol) was added. After stirring overnight at -35°C a sample (0.2 mL) was taken. The sample was quenched in 1 mL Et₂O saturated with water and filtered over a small plug of silica. The silica plug was thoroughly rinsed with the

wet Et₂O. Analyses on a DB-1 (J&W) GC column showed that the conversion was 55%. The reaction mixture was quenched with 20 mL of 1N HCl (aq) and the aqueous layer was extracted with Et₂O (3 × 25 mL) and the combined organic layers were washed with brine and dried over Na₂SO₄. Filtration and evaporation of the solvents yielded a mixture of **1c**, addition product and *n*-hexadecane which were separated by column chromatography (SiO₂, hexanes-ether: 5-1) giving 378 mg (2.2 mmol, 38%) of (*R*)-(-)-**1c**. $\alpha_D^{20} = -37.9^\circ$ (c = 1.97, CHCl₃). ¹H-NMR (200 MHz, CDCl₃): δ 2.5-2.8 (m, 4H), 3.4, (m, 1H), 6.1-6.2 (m, 1H), 7.0-7.1 (m, 1H), 7.2-7.4 (m, 5H). ¹³C-NMR (300MHz, CDCl₃): δ 33.64 (t), 40.91 (d), 44.81 (t), 126.64 (d), 126.94 (d), 128.72 (d), 129.73 (d), 143.13 (s), 149.47 (d), 199.15 (s). HPLC analysis (Chiralcel OJ, heptane-isopropanol: 95-5, flowrate 1.0 mL/min, $\lambda_{det} = 220$ nm) showed ee = 89%.